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## *Perspectives and Commentaries*

# Role of Antimicrobial Synergism in Infected Granulocytopenic Patients

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INFECTION continues to be a major cause of death in the cancer patient with granulocytopenia. Most often, these infections develop at mucosal sites damaged by cytotoxic therapy or on the skin following injury from invasive procedures. Early diagnosis is difficult since usual signs and symptoms are missing or minimal because of the granulocytopenia and other deficiencies of the inflammatory process. Fortunately, fever is almost invariably present since endogenous pyrogen is produced by macrophages irrespective of the reduced number of polymorphonuclear cells. This sign should be considered as early evidence of infection until proven otherwise [1, 2].

Among granulocytopenic (<1000/μl) cancer patients who develop new fever, 60% will ultimately be proven to have infection, of which 1/3 will be bacteremic. The spectrum of organisms causing these infections are wide and include most commonly *S. aureus, E. coli, Klebsiella* spp. and *P. aeruginosa.* Anaerobic bacteria are uncommon pathogens in this situation. These organisms are not necessarily the organisms that represent the normal flora for that area of the body from which they are isolated but are ones which occur following shifts of microbial flora during states of severe illness. About 50% of the infections will be caused by organisms acquired from the hospital environment [3, 4]. The acquired organism may be more virulent, certainly are more resistant to antimicrobial therapy than the normal flora, and may vary from hospital to hospital. In this journal, Todeschini and colleagues [5] described Gram-negative bacteremic infections in patients with hematologic malignancies. Most of these patients were granulocytopenic. The fatality rate associated with Gram-negative bacteremia was 53%. They also pointed out that septic shock, as well as inappropriate antibiotic therapy, was associated with the highest mortality rate. These observations serve to emphasize the importance of early, appropriate, empiric, antibiotic therapy to prevent septic shock.

But what is 'appropriate', empiric, antibiotic therapy for this high-risk patient population? Certainly, the infecting organism should be susceptible to the chosen antibiotic. In adition, recent evidence suggests that two antibiotics may be more beneficial than one. Combination therapy broadens the anti-bacterial spectrum to provide coverage for the wide range of possible infecting pathogens. In addition, it provides a synergistic killing effect against pathogens which also may be extremely important. In a prospective study evaluating three aminoglycosides, gentamicin, amikacin and sisomicin, in combination with carbenicillin for the treatment of infections in neutropenic cancer patients, it was shown that 52/63 (83%) patients improved when the infecting organisms were susceptible to both the aminoglycoside and carbenicillin compared to 60/90 (66%) responses for patients who received therapy in which the organisms were susceptible to only one of the antibiotics [6]. Klastersky and colleagues have shown that when infected cancer

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patients were treated with a combination of two antibiotics, the outcome was improved when this combination was synergistic against the infecting organism when compared with a non-synergistic combination (80 vs 49%) [7]. Similarly, Anderson *et al.* noted an improved outcome of patients with Gram-negative infections treated with synergistic antibiotic combinations and have correlated this beneficial effect with the severity of the patient's underlying disease. In a retrospective review of 173 Gram-negative bacteremias treated with two antibiotics for which the infecting organism was susceptible, these investigators found that patients without significant underlying disease did equally well (82–83%) whether ot not a synergistic combination was used. However, for patients with ultimately fatal underlying diseases, 82% improved when treated with a synergistic combination vs 61% improvement for those treated with non-synergistic combinations. For those patients with rapidly fatal underlying diseases, including many with cancer and granulocytopenia, 73% who received synergistic combinations improved vs 43% who did not ($P < 0.05$). Thus the advantages of a synergistic combination appeared to be greater for patients with more severe underlying diseases [8].

Similar findings have been obtained using bactericidal antimicrobial combinations for therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. For this patient population the primary determinant of a favorable outcome was the response of the patients' granulocytes during therapy. In a retrospective review of 67 patients who developed bacteremia, 27/29 (93%) responded to antibiotics if their granulocyte counts increased to greater than 100/$\mu$l during therapy. On the other hand, among the 38 patients who had no appreciable increase in their granulocyte count, 21 (55%) improved ($P = 0.006$). In this high-risk group of 38 patients whose granulocyte count remained below 100/$\mu$l, 0/4 patients responded when the pathogen was resistant to both antibiotics initially utilized for therapy, 6/14 (44%) patients responded when the organism was susceptible to one antibiotic and 15/20 (75%) patients responded when the organism was susceptible to both antibiotics used for therapy ($P < 0.025$) [9]. In a subsequent group of 75 high-risk patients with Gram-negative bacteremia, 8/18 (44%) responded if the combination was synergistic or partially synergistic against the infecting organism whereas 0/13 (0%) responded if there was no synergy [10].

These observations clearly demonstrate the importance of a two-drug combination for a small, but extremely important, high-risk subset of granulocytopenic patients, those patients with profound persistent granulocytopenia who develop Gram-negative sepsis. These studies also suggest that synergy may play an important role in the positive effect of these antimicrobial combinations. More patients, however, are required to determine if synergy is important for therapy against all types of Gram-negative bacteria or if it is important only for selected species.

There are many combinations of antibiotics which can provide synergistic activity and are appropriate for empiric therapy. The broad-spectrum anti-*Pseudomonas* beta-lactam antibiotics combined with the aminoglycosides have been particularly popular. The new beta-lactams mezlocillin, piperacillin, azlocillin, cefoperazone and moxalactam offer more activity against *Klebsiella* spp. than do carbenicillin and ticarcillin and are more likely to be synergistic with the aminoglycosides against these species while retaining their activity and synergy against *P. aeruginosa*. For the aminoglycoside component, amikacin may be beneficial if gentamicin- or tobramycin-resistant bacteria are identified as potential nosocomial pathogens [11]. In a large EORTC trial, azlocillin appeared more effective than ticarcillin, which in turn was more effective than cefotaxime, when each was used in combination with amikacin. Azlocillin was superior due to multiple ticarcillin-resistant (but azlocillin-susceptible) strains of Gram-negative bacilli. The explanation for cefotaxime's lesser efficacy is not readily apparent [12].

Recently there has been considerable interest in double beta-lactam antibiotic combinations. One such combination, moxalactam plus piperacillin, has been partially or occasionally synergistic *in vitro* against many of the bacteria infecting cancer patients and has the potential advantage of being less toxic. A controlled clinical trial comparing this regimen to moxalactam and amikacin has confirmed the safety of the regimen but was not large enough to evaluate fully its effectiveness in high-risk patients with Gram-negative sepsis [13]. Additionally, some double beta-lactam antibiotic combinations have not demonstrated enhanced protection in granulocytopenic animal models despite *in vitro* synergism [14]. At the present time the double beta-lactam combinations should be reserved for patients who have received several courses of aminoglycoside-containing regimens who may be at particularly high risk for developing nephro- or ototoxicity.

The mechanism whereby synergistic activity exerts its effect is not clear. Does synergy simply provide greater antibacterial activity in the serum? The degree of bactericidal activity or the

ratio of antibiotic concentration in the serum to the MIC of the infecting organisms has been shown to correlate with clinical outcome at a number of centers. Klastersky *et al.*, in addition to correlating the level of bactericidal activity in the serum and clinical response, has shown an association with bactericidal titers and the presence of synergy, between the antimicrobial agents used to treat the Gram-negative infections [15]. Gram-negative bacteria tend to regrow once the concentrations of antibiotics, particularly the beta-lactams, fall below the MIC. This high serum bactericidal activity may reflect the ability of a combination to lower the effective MIC or MBC, and thereby extend the time serum levels can be maintained above these levels. If this is the case, then the newer, broad-spectrum beta-lactam antibiotics may duplicate this high degree of activity in the serum and, therefore, be as effective as a two-drug regimen and avoid the toxicity of a second antibiotic. The currently available 'third-generation cephalosporins', however, may not meet these requirements. Cefoperazone does not have the beta-lactamase stability for nosocomial pathogens found in many institutions and neither cefotaxime, moxalactam nor cefoperazone have the amount of antipseudomonal activity required to be effective as single antibiotic therapy in this patient population. Controlled clinical trials using these agents have been performed but have not been large enough to evaluate effectiveness in high-risk patients, that is, those with persistent, profound granulocytopenia and Gram-negative bacteremia or with severe *Pseudomonas* infections [16].

Several experimental beta-lactams, such as ceftazidime and imipenem (thienamycin), have improved anti-*Pseudomonas* activity and are more likely to offer potential as single-agent empiric therapy. Controlled clinical data are not available at this time but in the granulocytopenic rat model, therapy with imipenem alone was equivalent to moxalactam plus amikacin for protection against the lethal effects of *Pseudomonas* sepsis [17–19]. In human volunteers both imipenem and ceftazidime singly provide better serum bactericidal activity against Gram-negative bacteria, including *Pseudomonas,* than that produced by a control regimen, ticarcillin plus amikacin [18, 19].

Alternatively, the importance of synergistic combinations may be in providing bacterial killing by two separate mechanisms of action, preventing the emergence of resistant strains of both. Using an *in vitro* system, Gerber *et al.* exposed *P. aeruginosa* to fluctuating levels of gentamicin in an attempt to stimulate serum levels in patients. They noted that gentamicin-resistant organisms developed during the experiment. These organisms were frequently small colony variants and were less pathogenic for normal and moderately leukopenic mice than were susceptible colonies. These small colony variants, however, invariably killed severely granulocytopenic mice challenged intraperitoneally. When injected into the thigh muscle of granulocytopenic mice, the resistant variants were unaffected by therapeutic plasma levels of gentamicin but were easily killed by ticarcillin. It was suggested by the authors that these resistant organisms may be, in part, responsible for gentamicin treatment failures in granulocytopenic patients infected with *P. aeruginosa*. Thus a combination of antibiotics, each with a different mechanism of action, may be important, particularly for aminoglycoside-containing regimens [20–22].

If the importance of synergy is simply to lower the effective MBC, then the newer agents may be satisfactory for treatment of the infected high-risk patient. On the other hand, if two antibiotics working through different mechanisms of action are important, then the single agent will be ineffective. Therefore results from studies of single vs combination regimens should be reviewed with care. Overall, single therapy with most of the newer agents should yield relatively satisfactory results. However, since only 5–10% of treated patients will have Gram-negative bacteremia, large controlled clinical trials will be required to evaluate adequate numbers of infected patients with profound, persistent granulocytopenia. It is in this population that we will learn whether or not a single, albeit very active, antibiotic is 'appropriate' as empiric therapy for the febrile, neutropenic patient. Until such data are available, it would be prudent to use combination antibiotic therapy in this severely compromised host.

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